REMARKS

In response to the Office Action of December 9, 2002, Applicants have amended the claims, which when considered with the following remarks, is deemed to place the present application in condition for allowance. Claims 33, 34, 68 and 69 have been canceled without prejudice. Favorable consideration of all pending claims is respectfully requested.

In the Office Action of December 9, 2002, claim 70 has been objected to as improperly dependent on claim 35. As presently amended, claim 70 no longer depends from claim 35. Withdrawal of the objection to claim 35 is therefore warranted.

Claims 19-36, 60-71, 85, and 96-99 have been rejected under 35 U.S.C.§ 112, second paragraph, as allegedly indefinite. As presently amended, claims 19-32, 60, 62-67, and 96-99 recite (or depend from a claim which recites) in relevant part: "[a] recombinant α-N-acetylglucosaminidase or fragment or derivative thereof wherein said α-N-acetylglucosaminidase or fragment or derivative thereof hydrolyzes α-N-acetylglucosamine residues from the non-reducing terminus of heparan sulphate." Claims 68 and 69 are presently canceled without prejudice from the present application. Withdrawal of the rejection of claims 19-36, 60-71, 85, and 96-99 under 35 U.S.C.§ 112, second paragraph, is therefore respectfully requested.

Claim 20 has also been rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. It is the Examiner's position that the metes and bounds of the phrase "in substantially pure form" is not clear. As presently amended, claim 20 recites "[t]he recombinant α-N-acetylglucosaminidase according to claim 19 in pure form relative to non α-N-acetylglucosaminidase material as determined by weight, activity, amino acid homology or similarity, antibody reactivity or other convenient means. Support for the amendment to claim

20 may be found throughout the specification, e.g., page 41, Example 8, "Purification of recombinant α-N-acetylglucosaminidase". In the example, the purification of recombinant α-N-acetylglucosaminidase is described as is the determination of purity via SDS-PAGE. Further support for the amendment may be found on page 29, line 29 to page 30, line 4. Withdrawal of the rejection of claim 20 is therefore respectfully requested.

Claims 29, 61, and 96-99 have been rejected under 35 U.S.C.§ 112, second paragraph, as allegedly indefinite. According to the Examiner, the metes and bounds of the phrase "substantially the same as" as recited in the rejected claims is not clear. As presently amended, claims 29, 61, and 96-99 no longer recite "substantially the same as." Withdrawal of the rejection of claims 29, 61, and 96-99 is therefore warranted.

Claims 32-34, 67-69, and 99 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. It is the Examiner's position that the phrase "amino acid sequence as substantially set forth in" does not contain clear metes and bounds. Claims 33, 34, 68 and 69 are presently canceled without prejudice. As presently amended, claims 32, 67, and 99 recite in relevant part "amino acid sequence as set forth in." Withdrawal of the rejection of claims 32-34, 67-69, and 99 under 35 U.S.C. § 112, second paragraph, is therefore respectfully requested.

Claim 71 has been rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite due to the recitation of "a patient suffering from α-N-acetylglucosaminidase." As presently amended, claim 71 recites in relevant part; "a patient suffering from α-N-acetylglucosaminidase deficiency or disorder." Withdrawal of the rejection of claim 71 under 35 U.S.C. §112, second paragraph, is therefore respectfully requested.

Claims 19-36, 60-68, 70-71, 85, and 96-99 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly directed to non-enabled subject matter. In response to the rejection and in order to advance prosecution of this application, Applicants have amended claims 19, 35, 60, 70, and 96 to recite α-N-acetylglucosaminidase or fragment or derivative thereof wherein said α-N-acetylglucosaminidase or fragment or derivative thereof hydrolyzes α-N-acetylglucosamine residues from the non-reducing terminus of heparan sulphate.

In addition, as presently amended, claim 32 recites in relevant part "an amino acid sequence as set forth in SEQ ID NO:2 or having at least 80% similarity to all or part thereof." Claim 85 has been amended to recite in relevant part: "the amino acid sequence set forth in SEQ ID NO:2 or having at least 80% similarity thereto and encoded by a nucleic acid molecule which is capable of hybridizing to the nucleotide sequence set forth in SEQ ID NO:1 or SEQ ID NO:3 under at least high stringency conditions." Withdrawal of the rejection of claims 19-36, 60-68, 70-71, 85 and 96-99 under the enablement provision of 35 U.S.C.§ 112, first paragraph, is therefore warranted.

Claims 19-36, 60-68, 70-71, 85, and 96-99 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly violative of the written description requirement. According to the Examiner, the rejected claims are directed to a genus of polypeptides derived from SEQ ID NO:2 including modified polypeptide sequences, modified by at least one of deletion, addition, insertion and substitution of an amino acid residue in SEQ ID NO:2 and fragments of SEQ ID NO:2 "that have not been disclosed in the specification." Office Action, page 7. It is the position of the Examiner that "[t]he genus of polypeptides claimed is a large variable genus including peptides which can have a wide variety of structure and function (specifically fragments and derivatives). Therefore many structurally and functionally unrelated polypeptides

are encompassed within the scope of these claims." Office Action, page 8. The Examiner alleges that the specification discloses only a single species of the claimed genus and that such disclosure is insufficient to put one skilled in the art in possession of "the attributes and features of all species within the claimed genus." Thus, the Examiner concludes that one skilled in the art could not reasonably believe that Applicants were in possession of the claimed invention at the time the present application was filed.

Possession of the invention may be shown by many ways. Actual reduction to practice is but *one* way to show possession. Possession may also be shown by a clear depiction of the invention in detailed drawings or in structural chemical formulas which permit one skilled in the art to clearly recognize that applicant was in possession of the claimed invention. Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶, "Written Description" Requirement, *Fed. Reg.* *66*(4):1099-1111, Friday, January 5, 2001/Notices, p. 1105. In addition, by disclosing sufficiently detailed, relevant identifying characteristics such as complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics, an applicant may show possession of the invention. *Id* at 1106.

It is respectfully submitted that the presently amended claims recite subject matter that was in possession of applicants as of the original filing date of the present application. The presently claimed fragments or derivatives of recombinant α-N-acetylglucosaminidase are defined in terms of function in that such fragments or derivatives hydrolyze α -N-acetylglucosamine residues from the non-reducing terminus of heparan sulfate. Support for such functional language appears throughout the specification, e.g., page 3, lines 5-7. Support for the

presently claimed active fragments or derivatives of recombinant α-N-acetylglucosaminidase may be found throughout the specification, e.g., pages 23-29 and Tables 2-3.

Thus, it is respectfully submitted that Applicants have disclosed sufficiently detailed, relevant identifying characteristics such as complete and partial structure (e.g., SEQ ID NO:2 and sequences having at least 80% similarity thereto), other physical and/or chemical properties (e.g., molecular weight of at least approximately 79 kDa to 89 kDa) , functional characteristics (e.g., the capacity to hydrolyze α -N-acetylglucosamine residues from the non-reducing terminus of heparan sulfate), coupled with a known and disclosed correlation between function and structure, and combinations of such characteristics, and have therefore demonstrated possession of the invention under the Written Description Guidelines of the U.S.P.T.O. Withdrawal of the rejection of claims 19-36, 60-68, 70-71, 85, and 96-99 under 35 U.S.C. §112, first paragraph, is therefore respectfully requested.

Claims 19-20, 26-29, 32-36, 85, 96, and 99 have been rejected under 35 U.S.C. §102(a) as allegedly anticipated by Zhao et al. (1995) "The gene encoding α-N-acetylglucosaminidase and mutations underlying Sanfilippo B syndrome" *American Journal of Human Genetics 5*: abstract 1059 A185 (hereinafter "Zhao et al. (a)").

Zhao et al. (a) report the cloning of a gene and cDNA potentially encoding human α-N-acetylglucosaminidase. The authors specifically state they accomplished this work "starting with the tryptic peptide sequence of enzyme purified from bovine testes." Nowhere in the abstract do Zhao et al. (a) disclose the production of a recombinant form of α-N-acetylglucosaminidase or a pharmaceutical composition comprising the same. The Examiner has stated that "[s]ince the enzyme has been isolated from a human source and is a recombinant enzyme," Examiner also takes the position that the glycosylation aspect, molecular weight, and the amino acid sequence

including the nucleotide sequence which encodes the enzyme are all inherent characteristics and that the enzyme disclosed in the reference and that claimed are one and the same. Applicants respectfully submit that Zhao et al. (a) provide no teaching for a recombinant form of α-N-acetylglucosaminidase. Applicants respectfully re-iterate that Zhao et al. (a) do not even disclose a cDNA and/or a peptide sequence. Although Zhao et al. (a) teach "[t]he N-terminus of the purified enzyme starts after a 23 amino acid signal peptide", it is respectfully submitted that "the purified enzyme" to which Zhao et al. (a) refer, is the enzyme purified from bovine testes, referred to six lines above in the same abstract. There is simply no teaching for a recombinant α-N-acetylglucosaminidase-- only a report for the characterization of a cDNA and genomic clone encoding the same, as well as mutational analysis of Sanfilippo B patients using SSCP analysis of PCR amplified segments of genomic DNA. Therefore, the presently claimed recombinant α-N-acetylglucosaminidase is distinct from both the purified bovine form of the enzyme and gene possibly encoding the human form of the enzyme, taught by Zhao et al. (a). Withdrawal of the rejection of claims 19-20, 26-29, 32-36, 85, 96, and 99 under 35 U.S.C. §102(a) is thus respectfully requested.

Claims 19-20, 26-29, 32-36, 85, 96, and 99 have been rejected under 35 U.S.C. §102(a) as allegedly anticipated by Zhao et al. (1994) "Sanfilippo syndrome type B: cDNA and gene encoding human α-N-acetylglucosaminidase" *American Journal of Human Genetics, 55*:A252, abstract 1473 (hereinafter "Zhao et al. (b)"). Zhao et al. (b) teach that α-N-acetylglucosaminidase was purified from bovine testes via ConA-, DEAE-, and phenyl-Sepharose chromatography, as well as SDS-PAGE without preheating. A 170 kDa band was selected for sequence analysis. Sequence data generated on the bovine form of the enzyme, revealed an internal 23 amino acid sequence, the ends of which were chosen for the design of

degenerate 17 base oligonucleotides and used for RT-PCR of human fibroblast RNA. A 41-mer synthesized from the sequence of the RT-PCR product was used to screen a human testes cDNA library. Ultimately, a cDNA for human α-N-acetylglucosaminidase was obtained. Use of the cDNA as a probe on a Northern blot of fibroblast RNA revealed a 3 kb mRNA. A significant deficiency of this mRNA in two MPS IIIB fibroblasts lines was also demonstrated.

It is respectfully submitted that there is no teaching for a recombinant α-N-acetylglucosaminidase in Zhao et al. (b). The authors reportedly teach that the cDNA encodes a protein of "743 amino acids (although some uncertainty remains about 93 nucleotides which may be intronic." This statement of uncertainty further indicates that a recombinant α-N-acetylglucosaminidase was not produced by Zhao et al. (b). Although the authors do state that "no homologous amino acid sequence has been found in a search of GenBank..." since no enzyme was produced, the enzyme could not have been sequenced, and this statement must be taken to mean that a *putative* amino acid sequence *based on the corresponding (and potentially incorrect) human cDNA codons* revealed no homologous amino acid sequence on the database. Therefore, the presently claimed recombinant α-N-acetylglucosaminidase is distinct from both the purified bovine form of the enzyme and gene reportedly encoding the human form of the enzyme, by Zhao et al. (b). Withdrawal of the rejection of claims 19-20, 26-29, 32-36, 85, 96, and 99 under 35 U.S.C. §102(a) is therefore respectfully requested.

Further with respect to the rejection of claims under 35 U.S.C. § 102(a), the Examiner has stated on page 12 of the Office Action that the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art, i.e., the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein. With respect to the α-N-acetylglucosaminidase purified

from bovine testis of the prior art, i.e., Zhao et al. (a) and Zhao et al. (b), Applicants respectfully submit that at least a recombinant form of the enzyme is different from tissue-derived sources. Example 8 of the specification teaches that the increased molecular weight of a recombinant produced enzyme is due to the addition of carbohydrate side chains.

It is axiomatic that anticipation under section 102 requires that the prior art reference disclose *every element* of the claims. *In re King*, 801 F.2d 1324, 1326, 231 USPQ 136, 138 (Fed. Cir. 1986). Thus, there must be *no* differences between the subject matter of the claim and the disclosure of the prior art reference. The corollary of this rule is equally applicable. The absence from the reference of *any* claimed element negates anticipation. *Kloster Speedsteel AB v. Crucible Inc.*, 793 F.2d 1565, 1571, 230 USPQ 81, 84 (Fed. Cir. 1986). Applicants' invention differs from Zhao et al. (a) and Zhao et al. (b) with respect to the novel features described above. Withdrawal of the rejection under 35 U.S.C. § 102(a) is therefore warranted.

Claims 21-25, 30-31, 60-71, 97-98 have been rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Zhao et al. (a) and Zhao et al. (b) as applied to claims 19-20, 26-29, 32-36, 85, 96, and 99 and further in view of the common knowledge in the art of molecular biology. In response to the rejection, Applicants repeat, reassert, and incorporate by reference the remarks set forth above with respect to the extent of teaching provided by Zhao et al. (a) and Zhao et al. (b). It could not have been obvious to "take the cDNA clone taught by the above references and subclone it in any of the host cells" since no cDNA sequence is provided by either of the cited references. Common knowledge in the art of molecular biology at the time the application was originally filed does not ameliorate the deficiency of teaching provided by Zhao et al. (a) and Zhao et al. (b). That the difference in molecular weight of the recombinant form of the enzyme versus a tissue-derived form is due to N-glycosylation (and not some other

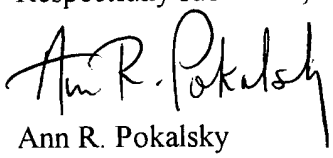
processing of the enzyme) was first revealed by the present application, not the prior art. Therefore, it could not have been obvious to one skilled in the art, unless he or she had the present application in hand, to obtain the presently claimed invention. Nor could it have been obvious to use a mammalian cell such as a CHO cell or express an α-N-acetylglucosaminidase as a fusion protein with a reporter molecule or a purification moiety without having the present application in hand. Likewise, use of a recombinant α-N-acetylglucosaminidase in the treatment of type B Sanfilippo syndrome could not have been obvious, since no sequence for a cDNA is provided and no recombinant protein is produced by the teachings of the cited prior art references.

At most, the combination of Zhao et al. (a) and Zhao et al. (b) with knowledge of molecular biology techniques at the time the application was originally filed, can only be cited for obviousness to try the presently claimed invention. "Obvious to try" however, is not the proper standard under 35 U.S.C.§ 103. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596, 1599 (Fed. Cir. 1988).

It is respectfully submitted that the Examiner has engaged in improper hindsight reconstruction in making the obviousness determination. Both suggestion and reasonable expectation of success must be found in the prior art, not applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). The authors' own uncertainty in Zhao et al. (a) concerning 93 nucleotides of the cDNA with respect to whether such nucleotides were intronic, coupled with a total non-disclosure of *any* nucleotide sequence for an α-N-acetylglucosaminidase in either Zhao et al. (a) or Zhao et al. (b), further indicate a lack of reasonable expectation of success found in the prior art. Withdrawal of the rejection of claims 21-25, 30-31, 60-71, 97-98 under 35 U.S.C. §103(a) is therefore respectfully requested.

In view of the foregoing remarks and amended claims, it is firmly believed that the present application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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